RECOMMENDATIONS OF THE SCIENTIFIC ADVISORY PANEL

HYDROCORTISONE ACETATE

CAS # 50-03-3
DECEMBER 8, 1994

Basis for ITSL:

A CAS- and NLM-online literature search was conducted for hydrocortisone acetate in February 1993, but it did not produce any relevant information to calculate an ITSL. The search found studies that focused on causing changes in immunologic cell ratios, or inducing enzymes. But none of the studies were by an appropriate route of exposure nor identified a no effect exposure level. Due to the lack of available toxicity data meeting the criteria of Rule 232(1), the ITSL for hydrocortisone acetate was determined to be 0.04 $\mu g/m^3$ with an annual averaging, based on Rule 232(1)(i).

Summary of Public Comment:

The only public comment received for this compound was from The Upjohn Company. They commented that other toxicological information was available to derive a screening level, rather than use the default value of 0.04 ug/m^3. This data consisted of a LD_{50} of >5 g/kg which was published in the company MSDS.

Response to Public Comment:

A complete reference check was conducted for hydrocortisone acetate, but because there was no information with which to derive an ITSL, hydrocortisone was also investigated. Hydrocortisone is the active portion of the hydrocortisone-acetate complex, with the acetate moiety used primarily to enhance solubility.

Upjohn provided an internal oral LD_{50} study for hydrocortisone. A total of 5 rats/group (sex and strain undetermined) were given a single oral dose of 2000, 2500, 3200, 4000, or 5000 mg/kg body weight of hydrocortisone, suspended in a 1% aqueous CMC vehicle. After an observation period of 7-days, only 2 deaths were noted in the highest dose group. A surrogate LD_{50} will be set at 4000 mg/kg, based on a shortened observation period and an undetermined LD_{50}. Additionally, because hydrocortisone is the active portion of hydrocortisone acetate, the screening level for hydrocortisone will be adjusted by the ratio of the molecular weights of these two compounds to account for the addition of the acetate group. Because no deaths were observed in the "surrogate LD_{50}", the ITSL derived by this method should provide a conservative estimate of the ITSL derived from an actual LD_{50}. However, if hydrocortisone acetate is absorbed to a greater degree than hydrocortisone, the LD_{50} for the acetate compound could be lower than that for hydrocortisone, lessening the amount of this conservatism.

The ITSL was derived as follows using Rule 232(1)(h):

hydrocortisone MW = 362 g/mol
hydrocortisone acetate MW = 404 g/mol

LD_{50} = 4000 mg/kg
W_A = Body weight of experimental animal in kilograms (kg).
I_A = Daily inhalation rate of experimental animal in cubic meters/day.
Since body weights and daily inhalation rates were not available, assume a default value of 0.931 m^3/kg.

$$ITSL = \frac{1}{500} \times \frac{1}{40} \times \frac{1}{100} \times \frac{LD_{50}\ mg/kg \times W_A}{0.167 \times I_A}$$

$$ITSL = \frac{1}{500} \times \frac{1}{40} \times \frac{1}{100} \times \frac{4000\ mg/kg}{0.167 \times 0.931\ m^3/kg} = 0.0129\ mg/m^3$$

$0.0129\ mg/m^3 \times 1000 = 13\ \mu g/m^3$

Molecular Weight Ratios:

$$\frac{13\ \mu g/m^3}{362\ g/mol} = \frac{x\ \mu g/m^3}{404\ g/mol}$$

$x = 14.5$ or $15\ \mu g/m^3$

Because of the many uncertanties in using an oral rat LD_{50} to derive an ITSL, the ITSL derived in this manner was compared to the therapeuptic dose level for hydrocortisone acetate. A therapeutic dose doesn't imply that the dose is safe from adverse effects. Hydrocortisone acetate is a glucocorticoid causing profound and varied physiologic effects at therapeutic doses. However, since the therapeutic dose is based upon human experience, such a comparison can help provide confidence as to whether or not the ITSL will be protective of public health. To make the comparison between the ITSL and the therapeutic dose, the ITSL was converted to a delivered dose as shown below. A comparison was made by determining the ratio of the therapeutic dose to the delivered dose. Therapeutic doses are not necessarily no effect doses. However, the ratio of calculated ITSLs and therapeutic doses were so large as to preclude, in the judgement of the committee, the existence of even a therapeutic effect at the ITSL.

COMPARISON OF DELIVERED DOSE[A] TO THERAPEUTIC DOSE

Compound Name	Proposed ITSL (ug/m3)	Therapeutic Dose[B] Range (mg/kg/day)	Delivered Dose (mg/kg)	Ratio of Doses[D] (Range)
hydrocortisone acetate	15	0.07 - 1.07[C]	0.004	18 - 268

A. Based on the formula: Delivered dose = {ITSL (mg/m3) x 20 m3}/70 kg

B. No implications are made that a therapeutic dose is a safe dose.

C. Hydrocortisone acetate injectable: 5-75 mg/treatment. Based on a 70 kg person = 5 mg/70 kg (or 75 mg/70 kg).

D. Therapeutic Dose/Delivered Dose = Ratio of Doses.

The ITSL for hydrocortisone acetate = 15 $\mu g/m^3$ based on annual averaging.